# Fasting Plasma Insulin Level Is an Important Risk Factor for the Development of Complications in Japanese Obese Children—Results From a Cross-Sectional and a Longitudinal Study

A.H.M. Waliul Islam, Shizuya Yamashita, Kazuaki Kotani, Tadashi Nakamura, Katsuto Tokunaga, Takeshi Arai, Makoto Nishida, Kaoru Kameda-Takemura, and Yuji Matsuzawa

**It is not known what types of factors may contribute to the development of complications in obese children. In the current investigation, we have performed a cross-sectional and a longitudinal study in Japanese obese children to clarify the relationship of the extent of obesity, fat distribution, insulin resistance, and aging to the development of obesity-related complications. In the cross-sectional study of 329 obese boys and 142 obese girls aged 7 to 15 years, the fasting plasma immunoreactive insulin (IRI) level was significantly higher than that of 46 non-obese boys and 48 non-obese girls (boys, 13.4 ± 6.7 *v* 4.9 ± 1.9 μU/mL, $P < .001$; girls, 14.0 ± 5.9 *v* 4.8 ± 1.8, $P < .001$). Linear regression analysis demonstrated that fasting plasma IRI correlated positively with fasting plasma glucose (FPG), triglycerides (TG), uric acid (UA), and systolic blood pressure (SBP) in obese boys, and with TG, SBP, and diastolic blood pressure (DBP) in obese girls, and negatively with serum high-density lipoprotein cholesterol (HDL-C) in both obese boys and girls. Multiple regression analysis demonstrated that fasting plasma IRI was independently and positively correlated with FPG, TG, and SBP in obese boys. Fasting plasma IRI in obese girls was positively correlated with TG, SBP, and DBP, and negatively with HDL-C. FPG decreased significantly in non-obese children at the onset of puberty, but it remained unchanged in obese children. Fasting plasma IRI and the IRI to glucose ratio increased with age in obese children, whereas they did not show any significant changes in non-obese children. Furthermore, in the longitudinal study of 42 obese children (32 boys and 10 girls) aged 7 to 15 years, significant increases in FPG ($P < .01$), insulin, UA, and SBP ($P < .001$, respectively) and a significant decrease in serum HDL-C ($P < .001$) were observed. Significant positive correlations were also noted between the yearly changes for IRI and SBP, and between the changes for IRI and the number of obesity-associated complications. These results suggest that fasting plasma IRI can be one of the most useful indices for predicting the development of obesity-associated complications in children, especially hypertension, hyperlipidemia, and hyperuricemia.**



IT IS WELL KNOWN that obesity is often associated with hypertension and various metabolic disorders such as non–insulin-dependent diabetes mellitus, hyperlipidemia, hyperinsulinemia, and hyperuricemia.[1-8] These complications have been demonstrated to accelerate atherosclerosis in obese subjects.[9,10] In adult obesity, an abnormal distribution of body fat rather than the degree of obesity has been shown to play a key role in the development of insulin resistance and to cause impaired glucose metabolism, atherogenic plasma lipid disorders, and hypertension.[11] One possible mechanism for insulin resistance may be the impairment of glucose utilization at the post–insulin receptor level.[12,13] However, mechanisms for the development of these disorders in obese people have not been clarified yet. A number of reports, including ours,[14] have shown that metabolic complications and hypertension are observed even in obese children. We previously reported the relationship between plasma insulin levels and systolic blood pressure (SBP) in Japanese obese children.[15] However, it remains to be determined what index may indicate the development of various complications in obese children. In the current investigation, we have performed a cross-sectional and a longitudinal study in Japanese schoolchildren to clarify the relationship of the degree of obesity, fat distribution, aging, and insulin levels to hypertension and metabolic disorders in childhood obesity. The purpose of the current study was to determine the most appropriate index for predicting complications of obesity in childhood.

## SUBJECTS AND METHODS

### *Subjects*

In the cross-sectional study, we studied 471 (329 boys and 142 girls) obese children aged 7 to 15 years who are living in Izumiohtsu City, Osaka, Japan. These obese children were selected according to data from an annual health examination by classifying children with a body weight more than 40% above the standard body weight as obese. Standard body weight was estimated by Hibi's normogram,[16] which is a weight-for-height chart for Japanese children based on a nationwide survey. Body mass index (BMI) (body weight in kilograms divided by height in meters squared) was considered the index for the degree of obesity in our study. As the control group, 241 non-obese boys and 218 non-obese girls aged 7 to 15 years whose BMI (mean ± SD) was 16.0 ± 2.0 in boys and 16.3 ± 2.3 in girls, were also studied and compared with the obese children. The profiles of investigated subjects are shown in Table 1. There were no differences in ages of these two groups. The average BMI of obese boys and girls was 25.9 ± 2.4 and 25.2 ± 2.3, respectively. Subjects were not given any treatment before or during this study. Legal written consent was obtained from the children and their parents before these examinations. A longitudinal study was performed by investigating changes in metabolic profiles and blood pressure in the 42 obese children (32 boys and 10 girls), who were selected from the subjects of the cross-sectional study and from whom a follow-up examination of more than 3 years

*From the Second Department of Internal Medicine, Osaka University Medical School, Osaka, Japan.*

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*Address reprint requests to A.H.M. Waliul Islam, MBBS, Second Department of Internal Medicine, Osaka University Medical School, 2-2 Yamadaoka, Suita, Osaka 565, Japan.*



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**Table 1. Profiles of Obese and Non-obese Children in the Cross-Sectional Study**

| | Obese | | Non-obese | |
|---|---|---|---|---|
| | Boys | Girls | Boys | Girls |
| No. | 329 | 142 | 241 | 218 |
| Age (yr) | 10.5 ± 2.7 | 10.3 ± 2.4 | 9.8 ± 2.0 | 10.5 ± 2.1 |
| Height (cm) | 142.5 ± 11.0* | 139.1 ± 10.8 | 131.1 ± 13.0 | 137.3 ± 12.6 |
| Weight (kg) | 53.5 ± 13.0* | 49.6 ± 11.5* | 28.2 ± 8.9 | 31.6 ± 9.6 |
| BMI (kg/m$^2$) | 25.9 ± 2.4* | 25.2 ± 2.3* | 16.0 ± 2.0 | 16.3 ± 2.3 |
| Waist (cm) | 81.9 ± 7.6* | 76.1 ± 8.5* | 60.0 ± 6.0 | 59.1 ± 5.7 |
| Hip (cm) | 87.7 ± 7.7* | 86.6 ± 8.5* | 76.9 ± 7.3 | 80.2 ± 7.3 |
| WHR | 0.93 ± 0.04* | 0.87 ± 0.06* | 0.78 ± 0.05 | 0.74 ± 0.05 |
| Triceps SFT (mm) | 25.8 ± 4.8* | 24.9 ± 4.2* | 12.5 ± 5.0 | 14.3 ± 5.5 |
| Subscapular SFT (mm) | 26.3 ± 8.2* | 24.8 ± 7.3* | 7.2 ± 4.0 | 8.8 ± 5.9 |

NOTE. Values represent the mean ± SD.
*Obese *v* non-obese, $P < .001$ (Student's *t* test).

was obtained. The average follow-up period was 4.8 ± 1.4 years. Their initial and final variables were used for the analysis.

### *Methods*

In the annual health examination conducted at the same facilities, height, waist circumference (at the level of the umbilicus), and hip circumference (at the level of the greater trochanter) were measured manually to the nearest 0.5 cm and body weight to the nearest 0.1 kg. Waist to hip ratio (WHR) was calculated from the two circumferences. Skinfold thickness (SFT) of the triceps and subscapular regions was measured by calipers (Meikosha, Tokyo, Japan).

Blood samples were drawn after an overnight fast. SBP and diastolic blood pressure (DBP), defined by the first and fifth phase of Korotkoff sounds, were measured in the supine position using a manual sphygmomanometer with a 12-cm cuff after 10 minutes' rest. This cuff was ordinarily used for non-obese adults and was considered suitable for measurement of blood pressure in obese children, since its use prevented the overestimation of blood pressure due to an inadequate cuff width.[17,18]

Anthropometric data and metabolic variables of the blood samples were obtained under similar conditions in 241 non-obese boys and 218 non-obese girls after matching for age. Serum total cholesterol (TC),[19] triglycerides (TG),[20] and uric acid (UA) levels were measured enzymatically. Serum high-density lipoprotein cholesterol (HDL-C) level was measured by the heparin-$Ca^{2+}$ precipitation method,[21] fasting plasma glucose (FPG) level by the glucose oxidase method, and immunoreactive insulin (IRI) level by radioimmunoassay. Fasting plasma IRI level for non-obese children was measured in 46 boys and 48 girls whose plasma was kindly provided by Dr Taku Yamamura from the Shinjo study (Nara). Serum γ-glutamyl transpeptidase (γ-GTP) and glutamic pyruvate transaminase (GPT) levels were measured by a bilirubin oxidase method and an International Federation of Clinical Chemistry (IFCC)-recommended enzymatic method, respectively.

### *Statistical Analysis*

Results are expressed as the mean ± SD. The significance of differences between obese and non-obese children was assessed by Student's unpaired *t* test. BMI, WHR, SFT, and IRI level were chosen as indices for the degree of obesity, fat distribution, indirect measure of body fat, and level of insulin resistance, respectively. Pearson's linear correlation coefficients were used to study the relationship between these indices and laboratory variables. Multiple regression analysis was also performed to quantify the effects of these indices. In the longitudinal study, initial and final values were compared by paired *t* test. TG and fasting plasma IRI were log-transformed before correlation and regression analysis. *P* less than .05 was considered statistically significant.

## RESULTS

### *Cross-Sectional Study*

Table 1 shows the comparison of clinical profiles between obese and control non-obese children. In obese boys, height was significantly greater than in non-obese boys ($P < .001$), but the difference was not significant in obese girls. Both obese boys and girls showed a significantly greater body weight than control non-obese children ($P < .001$, respectively). The mean BMI, WHR, and SFT in both obese boys and girls were significantly greater than in non-obese controls ($P < .001$). Furthermore, as shown in Table 2, more marked abnormalities in metabolic parameters and blood pressures were demonstrated in obese children than in non-obese children.

We further investigated FPG levels in relation to age in the two groups. As shown in Fig 1A and B, FPG level increased rapidly at the age of 12 in control non-obese children, and then subsequently decreased, remaining stable at a lower level after the age of 13 years. This age is considered the most common age of puberty in Japanese children. In contrast, FPG level remained almost constant from 7 to 15 years in both obese boys and girls.

We also investigated fasting plasma insulin levels according to age, and the results are illustrated in Fig 2A and B. Distinct differences were observed in the distribution of fasting plasma insulin levels between the two groups. Even at the early-elementary age, fasting plasma insulin levels were already higher in both obese boys and girls than in non-obese controls. Insulin levels gradually increased thereafter according to age, although they decreased slightly at the age of 13 years in obese girls. In contrast, in control non-obese children the fasting plasma insulin level stayed

**Table 2. Laboratory Data and Blood Pressure in Obese and Non-obese Children in the Cross-Sectional Study**

| | Obese | | Non-obese | |
|---|---|---|---|---|
| | Boys | Girls | Boys | Girls |
| FPG (mg/dL) | 92.3 ± 6.5 | 88.5 ± 7.0* | 92.2 ± 8.1 | 90.3 ± 8.6 |
| Fasting plasma IRI (μU/mL) | 13.4 ± 6.7† | 14.0 ± 5.9† | 4.9 ± 1.9‡ | 4.8 ± 1.8§ |
| TC (mg/dL) | 189.6 ± 33.6† | 184.1 ± 29.1† | 171.7 ± 22.6 | 173.5 ± 20.4 |
| TG (mg/dL) | 108.4 ± 46.4† | 105.8 ± 51.9† | 62.5 ± 19.6 | 66.1 ± 20.0 |
| HDL-C (mg/dL) | 52.8 ± 12.3† | 50.4 ± 9.2† | 65.6 ± 14.0 | 61.9 ± 11.9 |
| UA (mg/dL) | 4.2 ± 1.0† | 4.0 ± 0.8 | 3.9 ± 0.8 | 3.9 ± 0.8 |
| γ-GTP (U/L) | 16.2 ± 7.0† | 12.9 ± 5.3† | 10.0 ± 2.2 | 10.1 ± 6.9 |
| GPT (U/L) | 32.2 ± 28.2† | 22.2 ± 21.7† | 14.5 ± 4.8 | 12.2 ± 3.2 |
| SBP (mm Hg) | 119.0 ± 13.5† | 117.1 ± 14.4† | 107.5 ± 8.7 | 106.4 ± 9.1 |
| DBP (mm Hg) | 70.4 ± 9.8† | 71.1 ± 10.3† | 63.1 ± 9.4 | 64.7 ± 9.4 |

NOTE. Data are the mean ± SD.
*$P < .05$, †$P < .001$ (obese *v* non-obese, by Student's *t* test).
‡Measured in 46 non-obese boys in the Shinjo study.
§Measured in 48 non-obese girls in the Shinjo study.

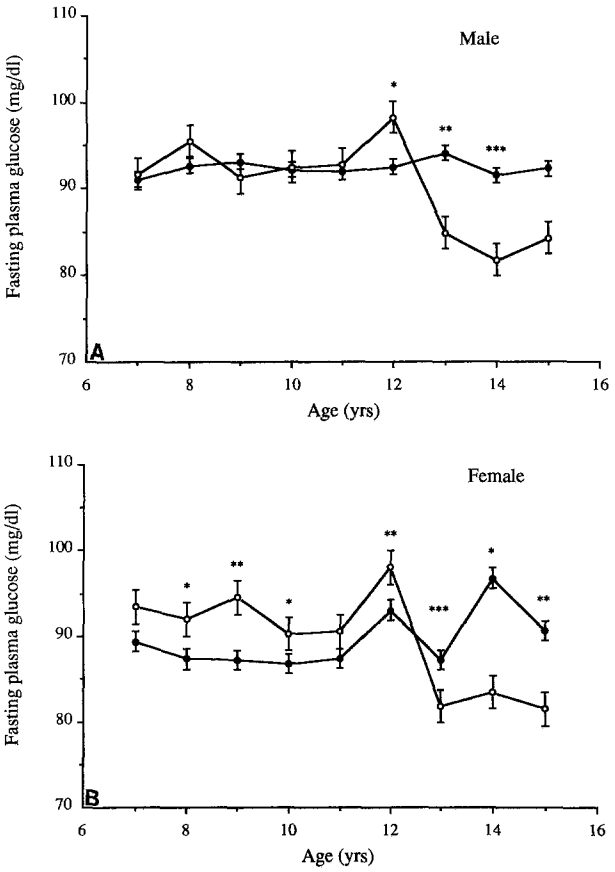


**Fig 1. Average FPG level at each age in (●) obese and (○) non-obese (a) boys and (b) girls. Bars represent the standard error. Sample sizes for FPG in obese boys were 27, 37, 38, 70, 66, 54, 14, 15, and 8; in obese girls, 18, 16, 24, 26, 21, 9, 9, 5, and 14; in non-obese boys, 28, 59, 28, 60, 19, 13, 21, 9, and 4; and in non-obese girls, 2, 51, 27, 49, 17, 23, 29, 14, and 6, respectively, for ages 7 to 15 years. *$P < .05$, **$P < .01$, ***$P < .001$.**

unchanged within the normal range regardless of age. We also studied age-related changes in the fasting plasma insulin to glucose ratio (Fig 3A and B), which was considered a better index for insulin resistance. Similar to fasting plasma insulin levels, the ratio was always greater and increased with age in obese children, whereas the ratio stayed unchanged at the low level in control non-obese children.

To elucidate factors that may contribute to the development of various complications associated with obesity, we determined correlation coefficients between metabolic indices and clinical variables by Pearson's linear regression analysis in obese children (Table 3). We found that fasting plasma IRI correlated positively with FPG, serum TG, and UA ($P < .05$, respectively) in obese boys. In obese girls, fasting plasma IRI correlated positively with TG, γ-GTP ($P < .001$, respectively), and GPT ($P < .01$). It was negatively correlated with serum HDL-C ($P < .05$ in boys, $P < .01$ in girls). Furthermore, fasting plasma IRI was correlated positively with SBP ($P < .01$) in boys and with SBP and DBP ($P < .01$) in obese girls. Correlations between clinical variables and other indices are also shown in Table 3.

We also studied the relationship of IRI with age, BMI, WHR, and triceps and subscapular SFT by a simple regression analysis. We found a significant correlation of fasting plasma IRI with age ($r = .279$, $P < .01$), BMI ($r = .387$, $P < .001$), and subscapular SFT ($r = .245$, $P < .05$) in boys, and with BMI ($r = .301$, $P < .01$) in obese girls.

After considering insulin level, age, and anthropometric indices as independent variables and clinical indices as dependent ones, we performed a multiple regression analysis to ascertain whether fasting plasma insulin independently correlated with the clinical variables without the effects of potential interacting factors such as age, degree of obesity (BMI), WHR, and SFT (Table 4). Partial regression coefficients showed independent positive correlations of IRI with FPG ($P < .001$), TG ($P < .05$), and SBP ($P < .001$) in obese boys. In obese girls, IRI showed a positive correlation with TG, γ-GTP ($P < .001$, respectively), GPT ($P < .05$), and SBP and DBP ($P < .05$), and a negative correlation with serum HDL-C ($P < .05$). Partial regression coefficients between other indices and clinical

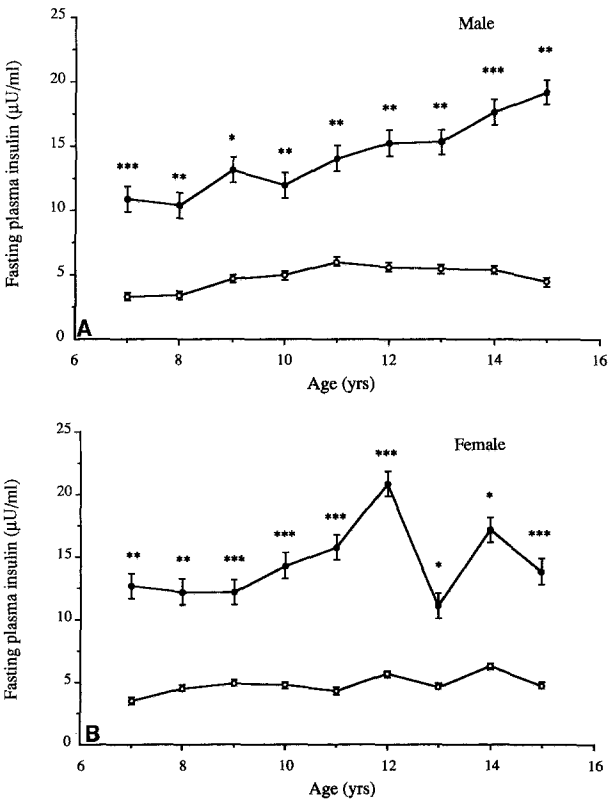


**Fig 2. Changes in fasting plasma insulin level at each age in (●) obese and (○) non-obese (a) boys and (b) girls. Bars represent the standard error. Sample sizes for fasting plasma insulin in obese boys were 27, 37, 38, 70, 66, 54, 14, 15, and 8, and in obese girls, 18, 16, 24, 26, 21, 9, 9, 5, and 14, respectively, for ages 7 to 15 years. For non-obese boys, they were 5 for each age group, except 6 for age 12 years, and for girls, they were 5 for each age, except 7 for age 8 years and 6 for age 15 years. *$P < .05$, **$P < .01$, ***$P < .001$.**

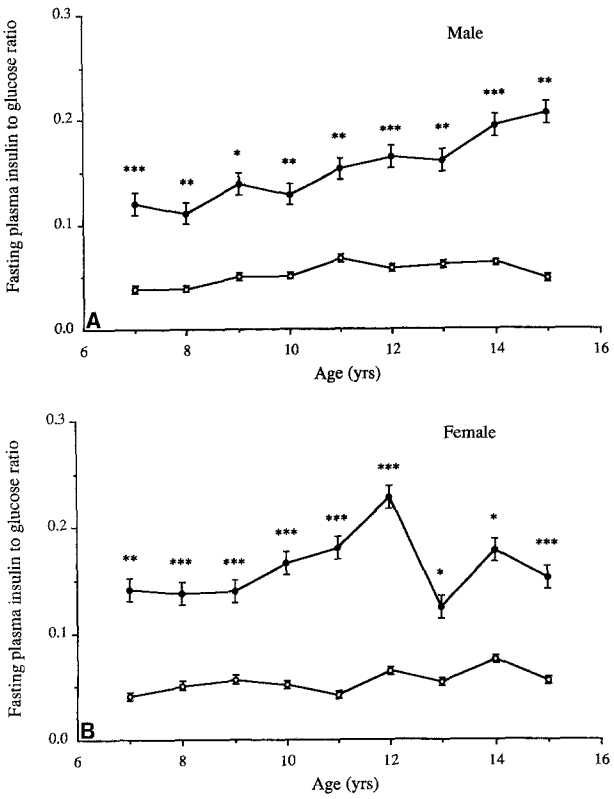


**Fig 3. Changes in the fasting plasma insulin to glucose ratio at each age in (●) obese and (○) non-obese (a) boys and (b) girls. Bars represent the standard error. Sample sizes for the fasting plasma insulin to glucose ratio in obese boys were 27, 37, 38, 70, 66, 54, 14, 15, and 8, and in obese girls, 18, 16, 24, 26, 21, 9, 9, 5, and 14, respectively, for ages 7 to 15 years. For non-obese boys, they were 5 for each age group, except 6 for age 12 years, and for girls, they were 5 for each age, except 7 for age 8 years and 6 for age 15 years. *$P < .05$, **$P < .01$, ***$P < .001$.**

variables are also presented in Table 4. Multiple correlation coefficients showed that the changes in all clinical variables except TC and HDL-C in girls could be explained by changes in fasting plasma insulin, age, BMI, WHR, and SFT in both sexes.

We performed Pearson's correlation analysis to elucidate further whether the adverse effects of insulin seen in obese children were also present in non-obese children. We found that plasma insulin was significantly correlated with FPG in boys but not in girls. Both age and BMI were also significantly correlated with UA ($P < .01$ in boys and $P < .05$ in girls), but no significant correlation was found among other indices and clinical variables in each sex.

*Longitudinal Study*

Little information has been obtained so far regarding age-related changes in metabolic parameters and blood pressure in Japanese obese children. In the current study, we have also performed a longitudinal study on the characteristic features of obese children. The data are summarized in Table 5. Although WHR and SFT did not change significantly during the follow-up period, significant increases in BMI, FPG, insulin, UA, and γ-GTP and SBP were observed in obese children. In contrast, serum HDL-C was significantly decreased in obese children.

Individual changes in fasting insulin levels are presented in Fig 4. Most obese children showed an increase in insulin level during the follow-up period. Furthermore, when the relationship between yearly changes in plasma insulin and in SBP was analyzed (by dividing the levels by the number of years of follow-up), we found a significant positive correlation between these two variables ($r = .465, P < .01$; Fig 5). A similar tendency was also observed between the yearly change in IRI and in DBP, although it was not statistically significant. We also tried to clarify whether fasting IRI levels will predict the development of complications associated with obesity. The number of complications was determined before and after the follow-up period. The metabolic parameters were considered abnormal as follows: FPG greater than 110 mg/dL, TC greater than 200 mg/dL, TG greater than 129 mg/dL, HDL-C less than 40 mg/dL, UA greater than 5.9 mg/dL (boys) and 4.9 mg/dL (girls), γ-GTP greater than 25 U/L, GPT greater than 20 U/L, SBP $\geqq$ 135 mm Hg, and DBP $\geqq$ 80 mm Hg in the initial and final examinations. The number of abnormalities was then calculated. When yearly changes in initial and final insulin levels were plotted against yearly changes in the number of complications (Fig 6), we found that the changes in fasting plasma insulin were significantly correlated with changes in the number of complications ($r = .425$,

**Table 3. Simple Correlation Coefficients Between Indices and Clinincal Variables in Obese Children**

| | Age | | BMI | | WHR | | Triceps SFT | | Subscapular SFT | | IRI | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Boys | Girls | Boys | Girls | Boys | Girls | Boys | Girls | Boys | Girls | Boys | Girls |
| FPG (mg/dL) | .012 | .148 | .005 | .230* | .032 | .126 | −.105 | .158 | −.089 | .055 | .226* | .190 |
| TC (mg/dL) | −.063 | −.110 | .082 | .003 | .063 | .055 | .126 | −.032 | .164 | .045 | .030 | .010 |
| TG (mg/dL) | .167 | −.010 | .191 | .149 | .126 | .055 | .063 | .032 | .141 | −.045 | .245* | .348‡ |
| HDL-C (mg/dL) | −.155 | −.032 | −.216* | −.133 | −.089 | .100 | −.110 | −.077 | .110 | −.077 | −.202* | −.266† |
| UA (mg/dL) | .423‡ | .421‡ | .478‡ | .479‡ | .200* | .045 | .010 | .179 | .226* | .197 | .224* | .122 |
| γ-GTP (U/L) | .195 | −.010 | .272† | .194 | .226* | .187 | .010 | .130 | −.110 | .289† | .155 | .395‡ |
| GPT (U/L) | .161 | .155 | .266† | .267† | .179 | .077 | .045 | .105 | .134 | .268† | .155 | .311† |
| SBP (mm Hg) | .355‡ | .286† | .360‡ | .419‡ | −.055 | .063 | −.032 | .202* | .055 | .249* | .315† | .295† |
| DBP (mm Hg) | .190 | .247* | .187 | .356‡ | .008 | .126 | .055 | .161 | .167 | .253* | .152 | .303† |

*$P < .05$.
†$P < .01$.
‡$P < .001$.

**Table 4. Multiple Regression Analysis Between Indices and Clinical Variables in Obese Children**

| | Standardized Partial Regression Coefficients | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Age | | BMI | | WHR | | Triceps SFT | | Subscapular SFT | | IRI | | Multiple $R^2$ | |
| | Boys | Girls | Boys | Girls | Boys | Girls | Boys | Girls | Boys | Girls | Boys | Girls | Boys | Girls |
| FPG (mg/dL) | −.054 | .043 | −.002 | .162 | .027 | .084 | −.067 | .187 | −.101 | −.099 | .318‡ | .165 | .097‡ | .138* |
| TC (mg/dL) | −.154 | −.295 | .170* | .166 | .002 | −.020 | .076 | −.070 | .101 | .170 | −.062 | −.092 | .064* | .057 |
| TG (mg/dL) | .059 | −.162 | .119 | .199 | .126* | −.036 | −.036 | .070 | .073 | −.186 | .168* | .354‡ | .102‡ | .170† |
| HDL-C (mg/dL) | −.133 | .212 | −.114 | −.178 | −.099 | .190 | −.063 | −.057 | .051 | .059 | .053 | −.250* | .064* | .104 |
| UA (mg/dL) | .202† | .266 | .321‡ | .321* | −.203‡ | .155 | −.069 | .007 | .215† | .030 | −.024 | −.087 | .334‡ | .293‡ |
| γ-GTP (U/L) | .118 | −.286* | .244† | .272 | .238‡ | −.016 | −.067 | −.053 | .048 | .257* | −.011 | .349‡ | .152† | .273‡ |
| GPT (U/L) | .037 | −.111 | .224† | .271 | .189† | −.063 | −.038 | −.142 | .029 | .242* | .029 | .259* | .103† | .194† |
| SBP (mm Hg) | .276‡ | −.037 | .157* | .372* | −.030 | −.023 | −.021 | −.017 | −.058 | .115 | .239‡ | .243* | .265‡ | .268‡ |
| DBP (mm Hg) | .190* | −.018 | −.079 | .310 | .005 | .041 | .061 | −.105 | .109 | .203 | .133 | .213* | .074† | .231‡ |

*$P < .05$.
†$P < .01$.
‡$P < .001$.

$P < .01$). Similar changes were observed between BMI and SBP ($r = .321$, $P < .05$) and the number of complications ($r = .554$, $P < .001$). Age had no effects on either the blood pressure or the number of complications. We also performed a multiple regression analysis to determine whether these associations reflected BMI and WHR. We found that changes in plasma insulin level were independently and positively associated with changes in SBP ($r = .384$, $P < .05$) without the potential effects of BMI and WHR.

## DISCUSSION

The current study has demonstrated that fasting plasma IRI levels are linked with blood pressure and various metabolic parameters in obese Japanese children. Fasting plasma IRI in obese children was found to be significantly higher than in non-obese children in both genders in the cross-sectional study. Fasting plasma insulin was further increased in accordance with age and sex, and this tendency was also confirmed in the longitudinal study. The increase in the fasting plasma insulin to glucose ratio in obese children suggests the development of insulin resistance in the course of continuation of obesity.

**Table 5. Profile and Clinical Variables in Obese Children in the Longitudinal Study**

| | Initial | Final | *P* |
|---|---|---|---|
| No. | 42 | 42 | |
| Sex (M/F) | 32/10 | 32/10 | |
| Age (yr) | 8.3 ± 1.3 | 13.0 ± 1.7 | <.001 |
| Height (cm) | 132.2 ± 9.0 | 158.6 ± 10.8 | <.001 |
| Weight (kg) | 43.5 ± 8.5 | 76.8 ± 16.1 | <.001 |
| BMI (kg/m²) | 24.6 ± 2.0 | 30.1 ± 3.4 | <.001 |
| Triceps SFT (mm) | 26.0 ± 4.1 | 25.4 ± 5.0 | NS |
| Subscapular SFT (mm) | 26.1 ± 8.7 | 28.1 ± 9.6 | NS |
| WHR | 0.92 ± 0.04 | 0.92 ± 0.04 | NS |
| FPG (mg/dL) | 88.6 ± 8.1 | 93.2 ± 7.6 | <.01 |
| IRI (μU/mL) | 15.0 ± 10.3 | 25.0 ± 13.0 | <.001 |
| TC (mg/dL) | 181.1 ± 27.2 | 180.5 ± 30.8 | NS |
| TG (mg/dL) | 115.7 ± 41.5 | 105.6 ± 47.3 | NS |
| HDL-C (mg/dL) | 54.3 ± 10.5 | 47.0 ± 7.5 | <.001 |
| UA (mg/dL) | 4.1 ± 1.1 | 4.9 ± 1.2 | <.001 |
| γ-GTP (U/L) | 16.2 ± 6.6 | 21.5 ± 12.0 | <.01 |
| GPT (U/L) | 34.1 ± 28.0 | 42.9 ± 44.2 | NS |
| SBP (mm Hg) | 113.3 ± 12.0 | 128.1 ± 13.4 | <.001 |
| DBP (mm Hg) | 68.9 ± 11.3 | 71.6 ± 10.8 | NS |

NOTE. Data are the mean ± SD. Significances of differences between initial and final observations are shown by *P* value (paired *t* test).

FPG in non-obese boys and girls decreased at about the age of puberty. This was probably due to changes in the levels of sex and growth hormones, which could affect carbohydrate metabolism.[22] In contrast to non-obese children, no significant changes in FPG were observed in obese children. These effects could be due to the less-pronounced effect of sex and growth hormones[23] or to the lack of pubertal changes in levels of these hormones. It is not clear whether the effects of age were confounded by developmental stage. In this regard, future investigation is necessary. However, FPG levels in obese boys did not differ from those in non-obese boys, suggesting the diminished effect of insulin due to insulin resistance, as seen in the obesity of adulthood. In obese girls, FPG level was significantly lower, possibly due to compensatory hypoglycemia caused by high levels of insulin.

There have been a number of reports regarding the relationship between insulin and plasma lipids.[10,24,25] Plasma IRI showed a positive correlation with TG and a negative

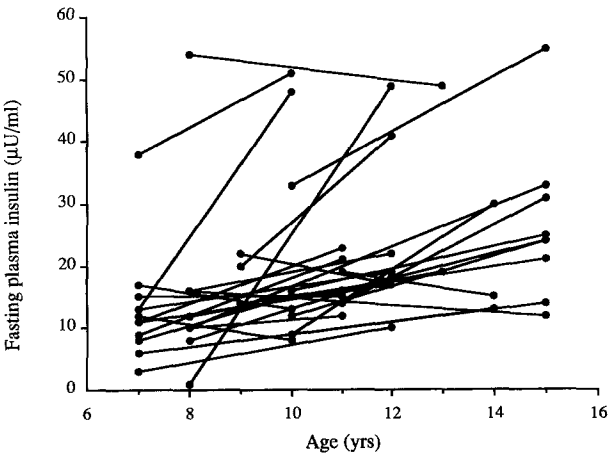


**Fig 4. Individual age-related changes in fasting plasma insulin levels in obese children in the longitudinal study.**

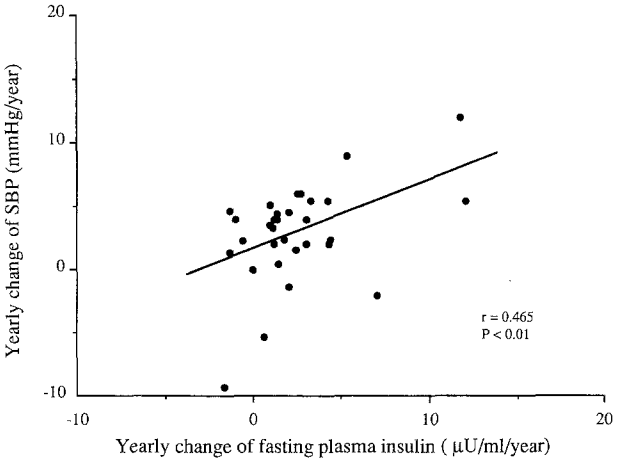


**Fig 5. Correlation between yearly changes in fasting plasma insulin and in SBP in obese children (n = 42). Oblique line represents the linear regression line, Y = 1.48 + 0.57X. Data were calculated by dividing the change in levels by the number of years of follow-up evaluation.**

correlation with HDL-C in our study. This might be due to a less-efficient stimulatory action of insulin on lipoprotein lipase and to the insulin-induced increase in production of very–low-density lipoprotein TG,[26] or to the impairment of insulin's inhibitory effect on hepatic very–low-density lipoprotein secretion.[27,28] The link between plasma insulin and serum UA observed in obese boys was previously described in subjects with hyperuricemia,[29] indicating that obesity-associated hyperuricemia begins to develop in childhood. The association of age and degree of obesity with UA may be due to maturation and/or biosynthesis of the purine derivatives for unknown reason,[30] or to increased androgenic activity in obese children.[31] The association of plasma insulin levels, BMI, WHR, and subscapular SFT with γ-GTP and GPT was thought to be due to fatty deposition of the liver.

The relationship of plasma insulin levels with blood

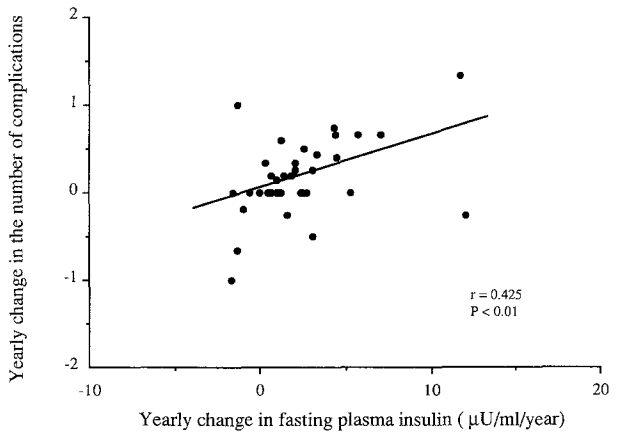


**Fig 6. Correlation between yearly changes in fasting plasma insulin and in the number of complications in obese children (n = 42). Oblique line represents the linear regression line, Y = 0.032 + 0.061X. Data were calculated by dividing the change in levels by the number of years of follow-up evaluation.**

pressure and metabolic variables in our cross-sectional study was consistent with previous reports.[22,32,33] Plasma insulin levels were significantly correlated with SBP in both sexes and with DBP in obese girls by simple and multiple regression analysis. Multiple regression analysis showed that this relationship was not the consequence of age, BMI, and WHR. Insulin may stimulate sodium reabsorption from the renal tubules,[34] or act indirectly on the sympathetic nervous system and angiotensin II–mediated aldosterone secretion.[35,36] Furthermore, insulin has been shown to accelerate the hypertrophy of vascular smooth muscle.[37,38] In addition to the insulin-hypertension relationship, the maturation level and sex hormones might have some effects on blood pressure.[39] We found that in the cross-sectional study, aging and the degree of obesity (BMI) were also responsible for the development of hypertension in Japanese obese children, but this relationship was not significant when we performed multiple regression analysis in the longitudinal study. Fat deposition in the upper body, which corresponds to WHR, did not correlate significantly with blood pressure, serum TC, and TG in the current study, although it was reported elsewhere.[40-42] The relationship between WHR and UA in obese boys was consistent with the report by Gillum.[41] The association of subscapular SFT with fasting plasma insulin in obese boys in our study is partially consistent with that reported by Voors et al.[33] In adult obesity, WHR, which reflects intraabdominal fat accumulation, is known to be associated with various metabolic disorders. However, we did not find any correlation between WHR and insulin and glucose levels in Japanese obese children. Therefore, the lack of significant correlations between WHR and SFT with most of the dependent variables indicated that the measure of fat distribution did not signify the risk of obesity-associated disorders in Japanese children.

Considering the importance of hyperinsulinemia, insulin resistance, and its relationship with hypertension and metabolic disorders in the obese children of our cross-sectional study, we performed a longitudinal study. Although fat distribution did not change with age, the degree of obesity, FPG, UA, γ-GTP, and blood pressure changed significantly, indicating the continuation of obesity-associated metabolic complications since childhood. We also found that WHR did not decrease with adolescence, as it does in others.[43,44] It could be that in the Japanese, hip circumference does not increase as much with adolescence as it does in other populations. The significant relationship between fasting plasma insulin level and blood pressure in our cross-sectional and longitudinal study has established a possible role of insulin in the pathogenesis of hypertension in Japanese obese subjects even in early childhood, although the insulin–blood pressure relationship is not uniform among the different ethnic groups.[45-48] In addition, the change in fasting plasma insulin level was correlated with the number of obesity-associated complications, indicating that fasting plasma insulin may predict the development of obesity-associated risk factors for atherosclerosis.

Even though we could not measure sex and growth hormone levels in these subjects, it appears from the

age-related changes in insulin and glucose levels that puberty had no effect on fasting plasma insulin and glucose levels in obese children, whereas these values were decreased significantly near the onset of puberty in non-obese children in both genders. These changes may reflect the effects of sex and growth hormones on carbohydrate metabolism. We could not directly evaluate the extent of insulin resistance in these obese children because of the large number of subjects and many other limitations. However, the age-related changes in fasting plasma insulin levels suggest that these obese children have already developed hyperinsulinemia and impaired glucose utilization due to insulin resistance. Furthermore, the exhaustion of pancreatic β cells has not developed, since the obesity was not of long duration in these children. Therefore, as reported previously,[12] the elevated insulin levels in children indicate the severity of insulin resistance.

From the viewpoint of our current study in obese and non-obese Japanese children, it is clear that plasma insulin levels rather than the degree of obesity or body fat distribution closely correlate with hypertension and metabolic complications such as hyperlipidemia and hyperuricemia, and tend to be worsened with the continuation of obesity. Taken together, we conclude that fasting plasma insulin can be used as an important index for the development of hypertension and metabolic disorders associated with obesity in children.

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